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MEDICAL STAFF CONFERENCE

Tolbutamide

Therapeutic Trials and Clinical Practice

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and Kenneth A. Woeber, Associate Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* All drugs are toxic; in clinical medicine we are concerned only with matters of degree. It is a basic matter of judgment in each patient whether the therapeutic advantages gained exceed the toxicity which actually occurs or the risk of the toxicity which may occur. Adverse effects of therapeutic agents may account for 10 to 15 percent of all hospital admissions. Medical Grand Rounds will be concerned today with one specific example of the difficulty in determining whether drug effectiveness outweighs possible drug toxicity as reflected in the current controversy about tolbutamide. We have asked Dr. Henry Bourne from the Division of Clinical Pharmacology to review and analyze this problem for us.

DR. BOURNE:† More than a decade ago the University Group Diabetes Program (UGDP) admitted the first diabetic patient into a massive clinical trial aimed at determining the effect of hypoglycemic agents on progression of cardiovascular disease in diabetes. In 1970, after ten years, treatment of more than 1,000 patients in 12 clinical centers throughout the United States, and expenditure of more than seven million dollars, the results became known. First in the newspapers, later in medical journals, physicians and diabetic patients read that tolbutamide and phenformin did not slow the progression of cardiovascular disease, but actually increased the rate of cardiovascular death.[1,2]

The weeping, wailing, and gnashing of teeth that ensued amounted almost to a religious war: Important gods had been defiled, including the practicing physician, the pharmaceutical industry, and the much-revered efficacy of modern drugs. More important, many diabetic patients and their physicians were anxious, confused, and frightened by the possibility that a drug they had been using for years might actually cause harm, rather than good.

Now, two years later, the smoke has begun to clear. A reasoned, critical appraisal of the UGDP study is now possible. Such an appraisal seeks answers to questions that must be asked about any clinical trial:[3,4] Are the goals of the study clearly stated? Was patient selection appropriate?

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Were treatment regimens randomly assigned? Were end points measured by an accurate, reproducible method? Were single or double-blind procedures necessary and, if necessary, were they carried out? These questions allow us to judge the scientific validity of a clinical trial.

The practicing physician, however, puts his question more bluntly: "So what? How can I use this scientific information to treat my patients?" The "So what?" question, of course, is the real bone of contention of the UGDP study. I propose to deal with this question directly, not only because it is important for treatment of diabetes, but also because the tolbutamide controversy is the best publicized example of a common difficulty in present-day therapeutics. This difficulty is created by the ever-expanding supply of potent chemical compounds designed for treatment of an ever-lengthening list of diseases or symptoms, the etiologic and pathogenetic aspects of which are poorly understood. Essential hypertension, rheumatoid arthritis, coronary artery disease, and mental depression figure prominently on this list, along with the cardiovascular complications of diabetes mellitus. Voltaire's oft-repeated dictum takes on a disturbing ring of contemporary truth: "Doctors pour drugs, of which they know little, for diseases, of which they know less."

The modern clinical trial represents a potentially effective way of dealing with such ignorance. The clinical trial is usually superior to "clinical experience": We remember, now that we know about vitamin B_{12}, that Sir William Osler prescribed arsenic for pernicious anemia.[5] But, if a published trial is to help a physician in making clinical decisions, he must understand the trial's results and conclusions, as well as their limitations. As the tolbutamide controversy has demonstrated, the methodological subtleties and statistical sophistication of a major clinical trial can make the most abstruse molecular biology appear comparatively simple. (At least the molecular biologists appear to agree that the genetic code has been deciphered.)

Thus, the clinician's "So what?" regarding a trial of oral hypoglycemic agents may have wider implications. I hope that a careful review of the UGDP study can raise questions about the clinical usefulness of therapeutic trials in general. It may turn out, in fact, that the stimulus to asking those questions is a major, if not intended, positive result of the UGDP study.

TABLE 1.—*Criteria for Entry Into the* UGDP *Study

1. No previous history of ketoacidosis
2. Diagnosis of diabetes no more than one year before entry into study (GTT or hypoglycemic therapy begun)
3. Physician's judgment of life-expectancy to be at least five years
4. Glucose tolerance test (Sum of four values greater than 500 mg per 100 ml)
5. Initial four weeks on diet alone:
   a. No major diabetic symptoms, including ketosis
   b. Must be able and willing to follow the study protocol

*Adapted from reference number 1.

The Study Itself

A major goal of the UGDP study was to evaluate the efficacy of hypoglycemic therapy in preventing the vascular complications of diabetes mellitus. The study's principal conclusion was that tolbutamide and phenformin actually increased the risk of cardiovascular death. Two questions are directly relevant to both goal and conclusion: 1. What disease was being treated? 2. Exactly how was it treated?

The Achilles' heel of almost any clinical study is often the selection of patients to be studied. The criteria used for acceptance of patients into the UGDP trial are summarized in Table 1. Reading them, we see that the patient population was by definition highly heterogeneous. As we shall see, this heterogeneity tends to vitiate the study's conclusions.

First, there was an attempt to obtain patients with maturity-onset diabetes (not prone to ketosis) who were newly diagnosed—that is, patients in whom a diagnostic glucose tolerance test was obtained or hypoglycemic therapy commenced not more than one year before entry into the study. Although diabetes is often a subtle, indolent disease, no attempt was made to screen out patients who already had major and widespread cardiovascular disease that might be a result of longstanding diabetes, and which was to be the major focus of attention during treatment. The proportion of such patients was, in fact, quite high (see below).

Patients judged to have life-endangering conditions which could kill them within five years were screened out since the effect of drug treat-

ment on life-expectancy was not an initial goal of the UGDP study. This judgment proved fairly accurate since less than 10 percent of the patients were, in fact, dead after five years. But this vague criterion allowed some clinics to have a 20 percent mortality and others practically zero.

The unusual criteria applied to the glucose tolerance test also guaranteed heterogeneity. In fact, one in twenty of the patients studied did not meet even this criterion.[1,6]

The final criterion in Table 1 was meant to guarantee that the patients should not have diabetic symptoms in the absence of hypoglycemic drugs, so that a placebo group could be included in the protocol. As a result, unfortunately, potential heterogeneity was not only quite likely but guaranteed to be missed. Many of the patients had been receiving hypoglycemic therapy before entering the trial, and it is well known that the appearance of severe hyperglycemia (and symptoms) may require more than a month to reappear. In addition, this criterion meant that the principal accepted indication for any hypoglycemic treatment—the patient's symptoms —was eliminated before the study began.

Subjects who met these criteria were assigned randomly to one of five treatment groups (Table 2). All subjects were to follow a uniform diet regimen. One group received an oral lactose placebo. Three of the other four groups without regard for the individuals' blood sugar concentrations were placed on standardized doses of hypoglycemic agents: A standardized dose of insulin (based on body surface area), 1.5 grams of tolbutamide per day, or 100 mg of phenformin per day. Whatever the reasons for this experimental design, it guaranteed that 60 percent of the patients would receive treatment unlike that recommended for any diabetic patient in ordinary clinical practice. The fifth group received whatever insulin dose was required to maintain "normal" blood glucose concentration.

The effects of these five treatment regimens on the concentrations of blood glucose were completely predictable from a knowledge of diabetes and human nature. Each treatment group, including the one receiving placebo, showed an initial drop in fasting blood sugar. The placebo, tolbutamide, phenformin, and fixed-dose insulin groups showed a gradual rise in blood glucose thereafter. Fasting blood glucose remained at low concentrations only in the group for which doses of insulin were varied specifically in order to produce normoglycemia.[1,2]

TABLE 2.—*Study Treatments

Treatment	*Dosage*
I. Lactose Placebo	Dosage schedules corresponding to those used for oral hypoglycemic agents.
II. Insulin Standard (U-80 Lente Iletin insulin)	10,12,14, or 16 units per day depending on the patient's body surface area.
III. Tolbutamide	1.5 grams per day (1 gram before breakfast and 0.5 gram before the evening meal).
IV. Phenformin	100 mg per day. 50 mg before breakfast and 50 mg before the evening meal. First week of study only 50 mg before breakfast.
V. Insulin Variable	As much insulin as is required to maintain "normal" blood glucose. The minimum dose is 5 units per day.

*Adapted from reference number 1.

The blood glucose results could hardly have come as a surprise. More surprising, in contrast, was the survival data summarized in Table 3. The proportion of patients who died, from all causes, was higher in the tolbutamide-treated group, although this difference was not statistically significant. The death rate from cardiovascular causes, however, was definitely increased—in fact, more than doubled—in the tolbutamide group. This result showed a high degree of statistical significance. The increased death rate in the tolbutamide group began to appear in the fifth year of the UGDP study.[1] A later publication showed[2] that the death rate in patients treated with phenformin was also higher than in the other groups. This result, too, was statistically significant. Hence the weeping, wailing, and gnashing of teeth.

Criticisms of UGDP Study

The many criticisms leveled at the UGDP study can be grouped under four headings:

1. *Methods and statistics.* Principal targets of many critics included the unusual glucose tolerance criteria for entry into the study; failure to obtain or adequately specify certain characteristics of the patients; analysis of mortality data on the basis of the treatment to which a patient

TABLE 3.—*Number and Percent Dead by Cause of Death in* UGDP *Study**

Treatment	Number at risk of death	Cardiovascular Cause	Other Causes	Entire Group
Placebo	205	10 (4.9%)	11	21 (10.2%)
Insulin standard	210	13 (6.2%)	7	20 (9.5%)
Tolbutamide	204	26 (12.7%)	4	30 (14.7%)
Phenformin	204	26 (12.7%)	5	31 (15.2%)
Insulin variable	204	12 (5.9%)	6	18 (8.8%)

*Data summarized from references 1 and 2. Cardiovascular causes of death included myocardial infarction, sudden death, other heart disease, and extracardiac vascular disease. For reasons noted by the UGDP investigators[2] the phenformin results are not strictly comparable to those in the other groups since this treatment was used in only 6 out of the 12 clinical study centers. Therefore, their tests of statistical significance of the increased death rate in the phenformin group were not applied to the data shown here but to results in the six clinics in which phenformin was used.

was originally assigned, despite a 12 percent dropout rate; changes in therapy in 83 of 823 patients; failure of a considerable number of patients to take drugs as prescribed; addition of the phenformin treatment group to the protocol after the first randomization had begun, leading to problems in comparing groups; the investigators' decisions to stop treatment with tolbutamide while continuing the remainder of the study; and, finally, controversial statistical methods. These issues have been discussed in detail by Feinstein.[6] The clinician may be interested in less esoteric questions.

2. *Unrealistic treatment protocols.* Three of the five treatment groups received fixed doses of tolbutamide, insulin or phenformin. These could not have been expected to produce a sustained decrease in blood sugar and, in fact, did not.

3. *Heterogeneity of the patient population.* The use of 12 widely scattered treatment centers, employing broad, vague criteria for selecting patients, led to widely differing baseline populations and death rates, the latter ranging from 19 and 26 percent in the two highest to 1 and 2 percent death rates in the lowest. As Feinstein says:[6] "Homogeneity of the population is a basic premise for the logical validity of statistical tests based on randomization; the validity of the tests cannot be assured if the population consists of a combination of markedly heterogeneous groups."

4. *Questionably random assignment of subjects to treatment groups, with possible weighting of the tolbutamide group with high-risk patients.* No critic has claimed that the actual assignment of patients into the five treatment groups was not an honestly random procedure. However, since chance alone could weight one or another group with an unusual population, it is clear that distribution of patients must actually *be* uniform as well. We know that a large number of patient characteristics can be associated with a greater likelihood of cardiovascular death. Were these characteristics significantly more common in the tolbutamide and phenformin groups? Unfortunately, the only reasonable answer to this question is, "Perhaps, but we will never know for sure."

Possible risk factors tabulated by the UGDP investigators[1] were present in a high proportion of patients admitted to the study, including: Hypertension (31 percent), lipid abnormalities (13 percent), angina pectoris (6 percent), electrocardiographic abnormalities (4 percent), history of digitalis use (6 percent), and evidence of disease of peripheral arteries (arterial calcification in 16 percent, intermittent claudication in 5 percent, and absence of one or more arterial pulses in 13 percent).

These multiple risks present numerous problems: (a) Many risks were inadequately defined or measured, including the notoriously elusive diagnosis of angina pectoris. As another example, the definition of significant electrocardiographic abnormality was changed during the study, reducing the overall percentage finally reported by a factor of three or four.[6] (b) A number of potentially important risk factors were not tabulated in the published data, although a considerable body of evidence suggests that family history, use of tobacco, or a past myocardial infarction contributes greatly to the risk of a later cardiovascular complication. (c) Those risk factors which were determined were dealt with as if they all had exactly the same significance, and as if a combination of two or more of them in one subject were not particularly important.

Feinstein undertook a painstaking investigation of the reported data, and suggested, as have other critics, that the tolbutamide group may have had a preponderance of several risk factors, especially those which were, in fact, associated with a high mortality rate. Four risk factors present in patients upon their entry into the study

TABLE 4.—*Distribution of Cardiovascular Risk Factors**

Risk Factor	Associated Death Rate Overall (percent)	Prevalence of Risk Factor In Treatment Group (percent)	
		Placebo	Tolbutamide
ECG Abnormal	33.3	3.0	4.0
Use of Digitalis	30.4	4.5	7.6
Arterial Calcification	22.4	14.3	19.7
Angina Pectoris	21.3	5.0	7.0

*Taken from Feinstein.[6]

(Table 4) had the highest association with the overall mortality rate, ranging from 21 to 33 percent as the study progressed. All four were present in a higher proportion of the patients in the tolbutamide group than in the placebo group (Table 4).

The UGDP investigators' answer to this criticism is a cogent one: in the tolbutamide group the increased mortality rate from cardiovascular causes remains even when all patients with any "cardiovascular risk factors" are removed from the calculations.[1] However, because so many other possible risk factors were not measured, their contention may not be valid.

Lessons of UGDP Study

The UGDP study, then, contains serious flaws, some of them irremediable. Should we, therefore, consider it a fruitless scientific debacle, best disregarded and forgotten? On the contrary, I submit that the practicing physician can learn several important lessons from the UGDP study, despite—and perhaps even because of—its obvious flaws.

Comparison of the results in the placebo with those in the variable insulin groups (Table 3) leads to an exceedingly important conclusion: Fair control of fasting blood sugar concentration achieved by flexible doses of insulin did not prevent death in a heterogenous group of patients with glucose intolerance. Therefore, the physician who uses insulin effectively to control blood sugar in an unselected group of patients with maturity-onset diabetes will not, on the average, prolong life. It is certainly possible that control of blood sugar concentration in some more homogeneous subpopulation of diabetic persons could slow the death rate, but such a subpopulation has yet to be defined. Despite all the qualifying phrases, this conclusion appears both scientifically valid and clinically relevant.

In contrast, the conclusion that oral hypoglycemic agents increase the risk of death from cardiovascular causes cannot be considered scientifically valid because of all the reasons outlined above. On the other hand, the *possibility* that oral hypoglycemic agents "cause" increased cardiovascular death is a very real one, and clinically highly relevant. It means, at the least, that future trials must test this possibility in a setting more relevant to the actual clinical use of tolbutamide and phenformin.

Here a parallel example may prove instructive. Let us assume for the moment that William Withering failed to discover the foxglove, and that ten years ago cardiac glycosides were first shown to increase myocardial contractility, although their other actions were poorly understood. Accordingly, a large multi-center trial was begun. Patients were selected on the basis of (a) no cardiovascular symptoms and (b) an unambiguous laboratory test suggesting poor myocardial contractility, such as a cardiothoracic ratio of greater than 0.5. They were randomized into two groups: One received placebo, the other 0.375 mg of digoxin per day. No provision was made for individualizing a patient's regimen, and the patients were followed until one group demonstrated a significantly greater death rate. The analogy with tolbutamide and the UGDP study is fair. The study's rationale, like that of the UGDP, would have been fairly plausible, and its methods might have proved impeccable. Nonetheless, it is a fair bet that the digoxin-treated group would die faster. In a setting where therapeutic goals are undefined and treatment is not changed to fit the individual patient, the drug's toxicity would probably outweigh its recognized beneficial effects on heart muscle.

The furor following such a digoxin trial might well cause one to lose sight of the potential clinical usefulness of digitalis. Certainly the rational clinical usefulness of tolbutamide and phenformin has received relatively short shrift in the controversy concerning these drugs and cardiovascular death. In his devastating critique of the UGDP study[6] Feinstein relegated his own opinion to a footnote. Ironically, he agreed essentially with the UGDP investigators: Oral agents should be used to treat *symptoms* from hyperglycemia; if they fail, insulin should be tried.

Who should take tolbutamide? This is really the "So what?" question leveled at the UGDP study by the clinician. I would approach this question by outlining two possible rationales for treating hyperglycemia, personified by physician A and physician B:

Physician A, concerned with preventing disease as well as treating it, seeks to prevent cardiovascular complications of diabetes by normalizing blood sugar. He will see that the UGDP study is irrelevant to his goal because the treatment protocol used for oral agents failed, predictably, to produce a sustained decrease in blood sugar concentration. He will recognize that adequate control of blood sugar concentration in a poorly selected population failed to prevent cardiovascular death (the variable insulin group), but he can claim that the results might be very different in a specific homogeneous group. Physician A will also admit that if he treats unselected patients with oral agents at a fixed dosage, without regard to their clinical response, he may run the risk of causing unnecessary cardiovascular death.

Physician B is more old-fashioned, seeking only to make his patients feel better. Unfortunately, he gets no help from the UGDP study either. The study is not relevant to his goal of ameliorating symptoms directly attributable to hyperglycemia because the patients were supposed to be free of symptoms before treatment started, blood sugar was generally not controlled with oral agents, and in the single group in which blood sugar was controlled, no assessment of symptomatic response was made (polyuria, cutaneous and other infections).

Defining Therapeutic Goals

In fact, the UGDP study presents little in the way of new clinical implications. The initial selection of patients and the unrealistic treatment regimens have made the study irrelevant to clinical practice. Still, in part because of these failings, the UGDP study may prove to have been well worth the trouble, because it should make us focus on the most crucial component of both therapeutic trials and every-day patient management: Clear definition of the goal (end-point) of treatment.

More specifically, the UGDP-tolbutamide controversy points up a fundamental difference between two kinds of therapeutic goals: Amelioration of signs and symptoms of a disease, and prophylaxis against possible future events. With oral hypoglycemics or any other drug, a physician must first decide which of these two goals he seeks, because the resulting therapeutic principles are quite different.

Before treating the signs and symptoms of any disorder, the physician first defines both his therapeutic end-point (how much better should his patient feel or function, and how fast must this be achieved?) and the upper limit of acceptable toxicity. During treatment, he can make repeated objective assessments of both efficacy and toxicity. In effect, the physician can often perform a valid therapeutic experiment, using the patient as his own control. In such circumstances, the scientific or physiologic rationale of therapy may not be clearcut, but empirical treatment can still be effective. An example might be the definite improvement in some of the symptoms of rheumatoid arthritis with salicylates although not until recently have we had any notion of how aspirin works.

Prophylactic treatment is quite different. The clinician's initial decision to institute treatment (whether tetanus toxoid to prevent tetanus or antihypertensive agents to prevent the sequelae of hypertension) must depend upon careful evaluation of evidence gathered in other patients, as well as the patient in his office. The candidate for prophylactic therapy must be representative of a homogeneous population in whom prophylaxis has proved effective. Furthermore, it will usually be impossible to prove whether prophylaxis was effective in the individual patient, unless it obviously fails. For this reason, the potential toxicity of the prophylactic regimen must be prevented if possible and detected as soon as it occurs. Even more important, in prophylactic treatment it is always useful to have an intermediate and easily measurable effect of drug treatment which can reasonably be related to the future events which the clinician aims to prevent (such as tests of blood coagulation in prevention of thromboembolism[7]).

The recently published Veterans Administration cooperative trial in treatment of hypertension[8,9] can provide an instructive contrast with the UGDP study. In the former study the level of blood pressure was used as an intermediate variable analogous to blood sugar in the UGDP study. Unlike that in the UGDP study, however, the patient population was stratified as to degree

of hypertension, and randomized to treatment with effective antihypertensive drugs or placebo. Provision was made for changing the drug regimen to fit the patient. In the treated group the blood pressure did come down and stayed down. Associated with the drop in blood pressure there was a sharp decrease in cerebrovascular accidents, renal deterioration, and death.

The point of this distressing contrast between the two studies is not that one showed good results of treatment, while the other did not, but that one (the hypertension study) was designed so that the results, whatever they might be, would be clinically relevant. As we have seen, this was not true of the UGDP study.

The question, "Who should take tolbutamide?" can best be answered by considering the goals of treatment in specific subgroups of patients with diabetes. Thus, a patient prone to episodes of ketoacidosis would receive neither symptomatic nor prophylactic benefit from tolbutamide, since there is little likelihood that the drug would control his carbohydrate metabolism. Similarly, the patient whose hyperglycemia has responded to diet alone does not need oral hypoglycemic agents since he lacks a proper end-point of therapy. In all of these categories, there is little disagreement. Any toxicity from an oral agent, given in a situation where it could not be useful, is unacceptable.

In 1972 many patients whose hyperglycemia is unresponsive to diet but who are totally asymptomatic undoubtedly are taking tolbutamide. Since no physician would justify such treatment in order to rectify laboratory values alone, hypoglycemic therapy in these patients must be (in theory, at least) prophylactic—that is, aimed at preventing future events. The voluminous and controversial literature[10] relating pharmacological control of blood sugar concentration to the prevention of cardiovascular complications of diabetes is far from convincing, especially if subjected to the kinds of criticism leveled at the UGDP study. I personally would withhold drug therapy in this group of patients while fully recognizing that eventually a subgroup of diabetic patients may be shown to have fewer myocardial infarctions and peripheral vascular occlusions, or less progressive retinopathy if given prophylactic hypoglycemic treatment.

For patients whose hyperglycemia *is* at present *symptomatic,* such as with increased infections, polyuria, polydipsia, or transient visual disturbances, an oral hypoglycemic agent (or insulin) is probably indicated. It should, of course, only be continued as long as both symptoms and blood sugar remain improved. In addition, it may be useful to stop the treatment periodically (every six to nine months) to determine whether it was really needed. Finally, it must be recognized that "secondary failure," or recurrence of hyperglycemia after initial improvement on drug treatment, will occur at various times in a high proportion of patients.[11] If this does occur, and if the patient truly needs normal blood sugar to prevent symptoms, he should then receive insulin.

The True Value of the UGDP Study

Despite all the criticism stimulated by the UGDP study, its real achievements should be measured in comparison with the explicitly stated goals of the UGDP investigators: 1. To evaluate efficacy of hypoglycemic treatments in prevention of vascular complications of diabetes; 2. To study the natural history of vascular disease in patients with maturity-onset diabetes not dependent on insulin; 3. To develop methods applicable to cooperative clinical trials.[1] As we have seen, the first two goals were compromised by heterogeneity of the patient population, possible nonuniform distribution of cardiovascular risk factors, and inappropriate treatment protocols. Nonetheless, the demonstration that control of blood sugar with insulin did not prevent cardiovascular death represents a real contribution to medical knowledge.

The contention that oral hypoglycemic treatment confers an increased risk of cardiovascular death cannot be considered proved by the evidence presented, primarily because we will never know whether cardiovascular risk factors were uniformly distributed among treatment groups. In retrospect, this problem could have been avoided by more careful definition and assessment of risk factors upon entry of patients into the study, perhaps combined with some stratification procedure (analogous to that employed by the Veterans Administration study of antihypertensive treatment). This then might have allowed comparison of results of treatments in comparable patient populations. Even here, however, the UGDP study has made a potential contribution to modern therapeutics by highlighting

an often neglected principle: Any potent drug administered in a rigid fashion, without regard to the patient's response, carries with it the possibility of serious toxicity but little possibility of benefit to the patient.

Finally, both in spite of and because of its faults, the UGDP study has indeed contributed to the future development of methods applicable to large cooperative clinical trials. We have learned the importance of relative homogeneity of patient populations, uniform and random distribution of specific patient variables among treatment groups, realistic treatment protocols applicable to medical practice, and the need for designing a clinical trial so that the practicing physician's "So what?" can be met with a straightforward answer. If we can use these lessons effectively in the future, the effort and expense of the UGDP study will not have been wasted.

TRADE AND GENERIC NAMES OF DRUGS

DBI-TD® ..... phenformin
Orinase® ..... tolbutamide

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BURNS IN THE ESOPHAGUS?—LOOK AT THEM

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—JOHN C. CARDONA, M.D., New York City
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